LARC Veterinarians' Guidance on Pain Management for UCSF Laboratory Animals.

LARC veterinarians work collaboratively with research investigators and the IACUC to provide the best possible pain management for animals, consistent with sound research. LARC veterinarians follow the guidelines of the American College of Laboratory Animal Medicine and the National Academies of Science. [1-4]

1. Some General Principles:

- Definitive diagnosis of pain is challenging in animals, especially if the diagnosis is based only on brief and few observations
- Animals may be experiencing pain even if the human observer does not detect it.
- Surgery must be assumed to be painful for at least 24 to 72 hours after the procedure, or even longer for more invasive procedures.
- Most surgical, and many chronic, pains have an inflammatory component.
- Multimodal analgesia that combines an anti-inflammatory analgesic (NSAID) with an opioid (most often: buprenorphine) and a local anesthetic-analgesic (bupivacaine or lidocaine) is recommended.
- Balanced anesthesia that includes agents with analgesic activity (ketamine, opioids, alpha-2 adrenergics) is also recommended.
- Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals. (United States Government Principles)[5]
- Effective and safe doses can vary with strain, sex, health status, age of the animal, with other drugs being administered, and with the procedure being performed.
    - Strain and genotype
    - Sex
    - Age of the animal
    - Health status
    - Other drugs being administered
    - The procedure being performed.
- Animal-use protocols may need to be modified as experience using particular drugs in particular animals for a particular procedure is gained.
- Anesthetics, analgesics, untreated pain, and inflammation all potentially introduce research variability into an experiment. Investigators should search the literature and consult with LARC veterinarians for demonstrated effects of pain and painkillers on specific models. Pilot work in the investigator's laboratory may also help identify whether pain and/or painkillers introduce unacceptable research artifacts.
- Careful tissue handling by skilled surgeons can reduce the potential for post-surgical pain.

2. Pain Recognition:

When to Assess Animal Pain:

Animals should be assessed for pain in the days and hours following surgeries, as well as for the chronic pain of cancer, inflammatory disease. Animals are at high risk for post-surgical pain during the night after their surgery, when no one may be there to assess them. It is best practice to evaluate animals when the last analgesic dose is near the end of its therapeutic window of efficacy (e.g., 8 – 12 hours after the last buprenorphine) and to re-dose if necessary.

- Assess animals in 'real time' for:
  o Presence of Pain-specific behaviors (spontaneous and evoked)
  o Reduction of normal behaviors
- Assess evidence of recent pain

Assessment of Pain in Rodents:

Whether looking for the onset of pain-related behaviors or assessing a decrease in healthy behaviors, investigators must first be familiar with the normal behavior of the species of animals, and when possible, the individual animals, they work with.

Pain-specific Behaviors in Rodents:
You may note (but these are not always evident):
- Twitching, Writhing, "Cat-arching" (depends on procedure) [link][link][link] [6, 7]
- Grimaces or "pain faces" (including squinty eyes and lowered ears) [link] [8]
- Hunched posture
- Vocalization (in response to handling)
- Chewing at surgical site
- Limping (depends on procedure)
- Shallow, rapid breathing (depends on procedure)

Reduction in Normal Behaviors:
- Not moving about normally
- Not interested in treats or in nesting material
- Not grooming, eating or drinking normally (Note: with people watching, many animals decrease these behaviors)
- If trained to take treats, have reduced interest in treats or are slower to take them.

Eliciting Evidence of Pain: after watching the animals' spontaneous behavior in the cage, encourage the animal to perform behaviors by:
- Giving fresh nesting material
- Giving preferred treats (placed so animal will move and stretch to retrieve them)

- Handling (assess vocalization)

Evidence of Recent Pain (that may be ongoing):
- Loss of Weight (grams)
- Loss of Body Condition (BCS Score) [link]
- Ungroomed coat
- Decreased fecal output
- Animals who normally build a good nest have not built a nest [link] [9]
- Porphyrin staining (rats)

3. Balanced Anesthesia:

Balanced anesthesia is the combination of two or more anesthetic agents to increase the desired effects and decrease side-effects. An injectable combination (typically, ketamine-xylazine or ketamine-dexmedetomidine) may be appropriate for some procedures, but adding an inhalant (typically, isoflurane) delivered via a precision vaporizer, allows titration minute-by-minute to a depth that is both safe and effective.

Some common agents that have anti-nociceptive (pain-killing) activity during anesthesia include ketamine, xylazine, dexmedetomidine, buprenorphine, lidocaine and bupivacaine. It is strongly recommended to use at least one of these during significant surgeries.

Some common agents that do NOT have significant anti-nociceptive (pain-killing) activity during anesthesia and do NOT contribute to post-surgical pain control include isoflurane, pentobarbital, acepromazine, midazolam, and tribromoethanol.

4. Preventive/Preemptive Multimodal Analgesia:

When pain is to be expected (such as with surgeries), LARC veterinarians recommend treating with analgesics preemptively, before signs of pain are evident. First, assure that no animal awakens from anesthesia after a surgery without administration of pain drugs. Continue treating for pain for at least 24 hours after surgeries, and longer for more invasive surgeries. To minimize inter-animal variability, consider treating all animals in the cohort with the same pain medications.

Multimodal analgesia is the combination of analgesic drugs with different modes of action. LARC veterinarians generally recommend using three classes of analgesic drugs for animal surgeries: an opioid (such as buprenorphine), a nonsteroidal anti-inflammatory analgesic (e.g., meloxicam, flunixin or carprofen) and a local anaesthetic/analgesic (such as bupivacaine or lidocaine).

5. Non-pharmaceutical adjuncts for pain management
- Insulative nesting material
- Increased ambient temperatures

- Shelter in the cage
- Soft food (easily accessed)
- Warmed parenteral fluids (subcutaneous or intraperitoneal)
- Compatible cage-mates [10]

6. Some Model-specific recommendations for Rodents:

The approach to pain management for surgeries will depend on the expected severity of post-operative pain for the particular surgery, as well as whether any drug classes (opioids or NSAIDs) must be avoided because they would interfere with research objectives

Several different approaches can meet the goals of preventive multimodal analgesia for surgical protocols. Doses for recommended drugs are posted [link to the IACUC or LARC website]

Remember that proper doses can vary with strain, sex, and age of the animal, health-status, with other drugs being administered, and with the procedure being performed. Pilot studies can be useful to adjust drug doses for the particular application.

A. Moderate Pain anticipated (examples):
- **Some Abdominal Surgeries**
- **Subcutaneous Osmotic Pump Placement**
- **Embryo transfer**
- **Skin transplantation/allograft**

B. Moderate Pain anticipated (but requires anesthesia for placement in device):
- **Stereotactic/Craniotomy Surgery in Mouse or Rat**

Note: placement in stereotactic unit is easiest if animals have received injected anesthetics, as an isoflurane face-mask can be dislodged while getting the animal positioned.

C. Severe Pain anticipated (examples):
- **Thoracotomy for cardiac manipulation**
- **Long-bone fracture and other orthopedic procedures**
- **Vertebral procedures**
- **Some abdominal surgeries (with organ manipulation)**
- **Trauma models**

For these most invasive surgeries, longer treatment with opioids and NSAIDs is recommended. Sustained-release buprenorphine can provide 48 hour analgesia or longer with a single injection and less handling stress to the animals.

D. Painful and Chronic Medical Conditions (examples):

- Some invasive and metastatic cancers
- Diabetic neuropathy
- Colitis
- Cecal-ligation puncture and other inflammatory models
- Some lung models
- Neuropathy and painful side-effects of some drugs (e.g., alloxan, streptozotocin, anti-neoplastic and anti-virals)
- Pruritus

Many medical models can lead to pain, even if no surgery is involved. Unlike surgical pain, the onset may be more gradual and the duration may be much longer. Chronic buprenorphine or NSAIDs for more than a few days' duration are rarely recommended for rodent models.

Non-pharmaceutical nursing care can help (see above). Clear endpoints must be defined in the protocol for timely intervention (for example, euthanasia)

7. References

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